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Association Between *Helicobacter pylori* and Pharyngolaryngeal Carcinomas: Role in Development and Prognostic Significance

Helicobacter pylori ve Faringolaringeal Kanserler Arasındaki İlişki: Gelişimdeki Rolü ve Prognozdaki Önemi

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Abstract

Helicobacter pylori is a worldwide common bacteria that infects humans. This Gram-negative microorganism is microaerophilic, spiral or curved shaped, and urease, catalase and oxidase-positive. It has the ability to live in the acidic environment of the gastric mucosa. It has been shown that *H. pylori* plays a role in the development of gastric ulcers and malignant lesions. Furthermore, it was reported that *H. pylori* may be a cause of several systemic illnesses such as cardiovascular, dermatologic, immunologic, neurologic, hematologic, ophthalmologic, gynecologic, endocrine, and hepatobiliary diseases. In addition, positive or negative correlations between *H. pylori* infection and rhinitis, sinusitis, adenoiditis or adenoid hyperplasia, otitis media, tonsillitis, or tonsil hypertrophy have been demonstrated in various studies in the literature. However, *H. pylori*'s role in the pathogenesis or association with these diseases remains controversial. Some studies reported that systemic immune and inflammatory responses against *H. pylori* might cause some systemic diseases as well as different types of malignancies. Although there are studies about the role of *H. pylori* in benign and malignant diseases of the upper and lower respiratory tract, further studies are needed to reveal the pathophysiological relationship between *H. pylori* infection and respiratory diseases. The aim of this review was to summarize the studies that reported either a positive or negative relationship between *H. pylori* and benign and malignant diseases of the respiratory tract.
Keywords: Prognostic significance, pharyngeal carcinoma, laryngeal carcinoma, laryngopharyngeal reflux, carcinogenesis

Öz

Helicobacter pylori dünyada yaygın olarak bulunan ve insanları enfekte eden bir bakteridir. Bu Gram-olumsuz mikroorganizma, mikroaerofilik, spiral ya da eğimli şekildedir ve ayrıca üreaz, katalaz ve oksidaz olumludur. Midedeki asidik ortamda yaşamını sürdürme özelliğine sahiptir. Günümüzde *H. pylori*'nin gastrik ülser ve malign lezyonlarda rolü olduğu ispatlanmıştır. Dahası, *H. pylori'nin* kardiyovasküler, dermatolojik, immünolojik, nörolojik, hematolojik, oftalmolojik, jinekolojik, endokrinolojik ve hepatobiliyer hastalıklar gibi çeşitli sistemik hastalıkların nedeni olabileceği bildirilmiştir. Ayrıca literatürde *H. pylori* enfeksiyonu ile rinit, sinüzit, adenoidit/adenoid hipertrofi, otitis media, tonsillit/tonsil hipertrofisi gibi benign üst solunum yolu hastalıkları arasında olumlu ya da olumsuz ilişki gösteren çok sayıda çalışma bulunmaktadır. Ancak *H. pylori*'nin patogenezdeki rolü veya bu hastalıklarla olan ilişkisi ile ilgili tartışmalar devam etmektedir. Bununla birlikte bazı çalışmalarda *H. pylori*'ye karşı oluşan sistemik immün ya da enflamatuvar yanıtın bazı sistemik hastalıkların veya malignitelerin nedeni olabileceği bildirilmiştir. Her ne kadar *H. pylori*'nin üst ve alt solunum yolu benign ve malign hastalıklarındaki rolü hakkında çalışmalar bulunsa da, *H. pylori* enfeksiyonu ve solunum yolu hastalıkları arasındaki patofizyolojik ilişkiyi ortaya koymak için daha ileri çalışmalara gereksinim bulunmaktadır. Bu derleme ile literatürde *H. pylori* ve solunum yollarının hem benign hem de malign hastalıkları arasındaki hem olumlu hem de olumsuz ilişkiyi gösteren çalışmaların özetlenmesi hedeflendi.
Anahtar Kelimeler: Prognostik önem, faringeal karsinom, laringeal karsinom, laringofaringeal reflü, karsinogenez

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Introduction

Helicobacter pylori is a microaerophilic, curved or spiral-shaped Gram-negative microorganism with four to six flagella. It was discovered by Marshall and Warren in 1984. It is a urease-, catalase-, and oxidase-positive bacterium. *H. pylori* is actually sensitive to acid, but its motility and ability to convert urea to ammonium using urease provide a basic environment that protects it from the harmful effects of the acidic environment of the gastric mucosa[1,2].

Urease, flagella, adhesion factors, vacuole cytotoxins, cytotoxin-associated gene A (*cagA*) product, vacuolating cytotoxin A (*vacA*), outer inflammatory protein A (*oipA*), and duodenal ulcer-promoting gene A (*dupA*) products are the presumed virulence factors of *H. pylori*. Cytotoxin-associated gene A is the most important pathogenic factor and indicator of pathogenicity. However, it does not exist in all strains of *H. pylori*[2]. Cytotoxin-associated gene A is a highly immunogenic protein and rates of its seropositivity may vary in different countries (100% in east Asia, 50% or less in Western countries). In contrast, *oipA* is an outer membrane protein and works with *cagA* to organize intracellular signaling pathways. Duodenal ulcer-promoting gene A is a novel virulence factor whose function is not fully understood, but it is thought to be associated with duodenal ulcer and gastric cancer[2-5].

The stomach is known to be the natural reservoir for *H. pylori*. In the light of this knowledge, the association between *H. pylori* infection and some gastrointestinal malignancies has been demonstrated in different studies[1,6,7]. However, the potential relationship between *H. pylori* and malignancies of extra-gastric sites still remains controversal[2,8-12].

In this review, we aimed to summarize the studies that explore either positive or negative correlations between *H. pylori* and benign and/or malignant pharyngolaryngeal diseases.

Materials and Methods

A systematic search of the medical literature was conducted on 24.01.2018 by searching PubMed, Cochrane Library databases, and Google Scholar via the search terms "*Helicobacter pylori*", "helicobacter and pharyngeal and benign", "*Helicobacter* and laryngeal and benign", "*Helicobacter* and pharyngeal and malignant", "*Helicobacter* and laryngeal and malignant", "*Helicobacter pylori* and cancer". Among these articles, the articles which best clarify either positive or negative relationships between *H. pylori* and pharyngolaryngeal benign lesions and carcinomas were chosen.

Epidemiology and Pathogenesis

H. pylori infection is one of the most common bacterial infections in humans, affecting more than half of the world's population[13]. Its prevalence is 30-40% in developed countries and reaches up to 80-90% in underdeveloped countries[14,15].

The stomach is accepted as a natural reservoir for *H. pylori,* while tissues such as the gallbladder, gingiva, oral lesions, and dental plaques are shown to be potential extra-gastric reservoirs[8]. Furthermore, recent studies suggest that *H. pylori* can also be located in nasal polyps, the nasal and/or sinus mucosa, saliva, oropharyngeal aphthous lesions, adenotonsillar tissue, pharyngeal lymphoid tissue, and larynx[9-12].

The colonization and accumulation of *H. pylori* in different regions of the body highlights the importance of transmission route and progress of *H. pylori*-related infections. Although the dominant transmission route of *H. pylori* has not been determined, probable routes of contamination are fecal-oral, oral-oral, and gastric-oral (*e.g.,* reflux, vomiting)[2]. The infection is generally acquired during childhood (<10 years) and can remain silent for life. Only 20% of all infected patients develop symptoms due to their infections. The possible infection and manifestation of symptoms are related to environmental, bacterial, and host factors[2,11,16].

Extra-gastric diseases may be associated with increased systemic immune and inflammatory responses against *H. pylori*. A role and/or the potential relationship between *H. pylori* and the pathogenesis of several systemic diseases (such as cardiovascular, dermatologic, immunologic, neurologic, hematologic, ophthalmologic, gynecologic, endocrine, and hepatobiliary diseases) has been demonstrated[17-19].

It is known that *H. pylori* is the most common cause of chronic gastritis and gastric and duodenal ulcers in humans. It has also been demonstrated in numerous studies that *H. pylori* infection is a major risk factor for the development of several gastrointestinal malignancies (*e.g.,* gastric cancer, extra-gastric intestinal malignancies, gastric mucosal-associated lymphoid tissue lymphoma)[1,2,6,7]. It is categorized as a group 1 carcinogen by the International Agency for Research and recognized as an etiologic factor for gastric cancer by the World Health Organization in 1994. This bacterium may cause these diseases by destroying the defensive shield of the stomach and duodenum, leading to damage of these parts by digestive fluids. *H. pylori* has the ability to regulate transcription and folding of or gene transport by *cagA* protein and vacuolating cytotoxin and to induce neutrophil-dependent gastric mucosal cell damage and cell apoptosis[16].

The exact pathophysiologic mechanism for *H. pylori*-associated carcinogenesis has not been well defined even in gastric cancers[2]. However, *H. pylori* infection is known to provoke histological changes such as intercellular junction destruction, apoptosis, epithelial cell proliferation, and malignant transformation in the long term. In gastric diseases, the outcomes of *H.*

pylori infection are related to environmental factors (gastric microbiota, smoking, high sodium diet, serum iron level, long-term use of proton pump inhibitors), genetic polymorphism of the host, and virulence of the bacteria[20].

H. pylori is characterized by a high level of genetic diversity and has been implicated for regional DNA hypermethylation in gastric cancer. It was reported that methylation ratio declined significantly after *H. pylori* eradication. *H. pylori* strains in an individual may change over time due to DNA rearrangements, recombinations, and endogenous mutations. Bacterial virulence factors *cagA*, *vacA*, *dupA*, and the outer-membrane protein BabA have been reported to play key roles in *H. pylori*-induced gastric carcinogenesis[21,22].

It was shown that in the early phases of chronic inflammation, *H. pylori* induces apoptosis and cellular proliferation on the gastric mucosa whereas apoptosis is inhibited and cellular proliferation increases progressively during the process of malignant transformation. Also, increased gastric epithelial cell proliferation associated with *H. pylori* infection is one of the triggers for carcinogenesis. It has been observed that *H. pylori* may cause genetic instability via double-stranded DNA breaks or can induce gene activation and silencing through epigenetic pathways, but the mechanisms are not completely understood. The pathogenesis of genetic instability in *H. pylori* infections is complex, and either inflammation-induced reactive oxygen species or reactive nitrogen species are thought to play important roles[23,24].

As in the gastric mucosa, it is suggested that *H. pylori* may colonize the laryngeal and/or pharyngeal mucosa and may also cause increased epithelial cell proliferation resulting in carcinogenesis in the mucosa of the larynx/pharynx[23]. However, the pathogenicity or role of this bacterium in upper and lower respiratory diseases is still debated[2]. In particular, the pathophysiological correlation between *H. pylori* and lower respiratory tract infections *have* not been proven yet. Moreover, contradictory findings have been reported in the literature regarding the correlation between *H. pylori* and upper respiratory tract diseases, either benign or malignant in nature. Further studies are needed to reveal the pathophysiological relationship between *H. pylori* infection and respiratory diseases.

Reservoirs of *Helicobacter pylori* in the Upper Respiratory Tract and Diagnostic Tests

In the literature, numerous articles have reported different results regarding the correlation between *H. pylori* infection and rhinitis, sinusitis, adenoiditis or adenoid hyperplasia, otitis media, tonsillitis or tonsil hypertrophy. As a result of these studies, the pathogenicity and/or possible role of *H. pylori* remains controversial in this diseases[10,17,25]. The discordance in these studies may be related to difference in sample quantity, study design, or methodology. Diagnosis of *H. pylori* infection is not easy and there are several noninvasive (urea breath test, serological tests, stool tests, and molecular examinations) and invasive (endoscopic image, histology, rapid urease test, culture, and molecular methods) diagnostic tests available for its detection[1,2,26]. Each method has its own advantages, disadvantages, and limitations. The choice of one method or another varies on availability and accessibility of diagnostic tests, level of laboratories, clinical conditions of patients, and likelihood ratio of positive and negative results in different clinical circumstances[2]. Among these methods, nested- polymerase chain reaction (PCR) provides excellent specificity and sensitivity (>95%) and facilitates the detection of several target genes, including *ureA*, *glmM*, *ureC*, 16S rRNA, 23S rRNA, *hsp60*, and *vacA* genes for the detection of *H. pylori*[2,27]. Immunohistochemistry and PCR analysis are accepted as definitive methods for the diagnosis of *H. pylori* infection. Urea breath test is also a useful method for the follow-up of eradication. Serological tests for detecting *H. pylori* infection include measurement of antibodies [immunoglobulin (Ig) IgA, IgM, and IgG] against *H. pylori* antigens. These tests can show only the existence of *H. pylori* infection. However, serological studies may not be appropriate in developing countries since approximately 80% of the population is infected with *H. pylori* early in life. In addition, there is no single test that is regarded as the golden standard for *H. pylori* detection; therefore, the usage of combined tests is still preferred[1,3,28].

Role of *Helicobacter pylori* in Benign Laryngeal Lesions

The effect of *H. pylori* in different benign laryngeal diseases is under investigation, but the data in this field are still limited. Available data show that *H. pylori* cannot be considered as a member of the normal laryngeal flora, and recent studies are intended to reveal the role of *H. pylori* in laryngeal diseases[2,29].

Laryngopharyngeal reflux (LPR) is one of the most common diseases of the larynx which involves passage of gastric content through the upper esophageal sphincter, causing inflammation in the upper airways. The symptoms, diagnosis, diagnostic methods, and treatment modalities for LPR are well defined[30]. In a systematic review and meta-analysis, the prevalence of *H. pylori* among patients with LPR was 43.9%. The prevalence rate was identified by meta-analysis of 13 publications which were found valuable for quantitative analysis. But the majority of studies (10 of 13) were performed in Southeast Europe and Western Asia, rregions with higher overall *H. pylori* prevalences. The authors noted that despite a rate of 43.9% positivity, the recommendation to test for and treat *H. pylori* in LPR patients

remains uncertain due to the variability of *H. pylori* prevalence among countries. However, it is known that eradication of *H. pylori* significantly reduces some symptoms of LPR. Therefore, the authors of the review concluded that further studies including a wide range of geographic locations and homogenous study groups are needed to clarify the relationship between LPR and *H. pylori*[31].

Another study investigated the relationship between *H. pylori* and benign laryngeal lesions in 55 patients with vocal fold polyps (n=21), vocal fold nodules (n=14), or papillomatosis (n=20). Patients with LPR symptoms were excluded. Tissue specimens were analyzed by in-house PCR, and *H. pylori* DNA was detected in 5 of the 55 patients (9.09%). In another study, *H. pylori* DNA positivity was determined by real-time PCR in 58.6% of larynx samples and *cagA* gene was identified in 82.4% of benign laryngeal lesions[12,32].

Association Between *Helicobacter pylori* and Laryngeal Cancers

Clinical and/or experimental data indicate that inflammation and chronic infection are the most important epigenetic and environmental factors that lead to tumor progression and tumorigenesis. Because *H. pylori* has been identified as a significant carcinogenic factor in gastric cancers, its role in the pathogenesis of laryngeal squamous cell carcinoma (SCC) is under investigation[23,29,33]. Laryngeal carcinoma accounts for approximately 25% of all the carcinomas of the head and neck, and 2-3% of the carcinomas in the whole body. It is also known that the larynx is the sensitive site of the upper gastro-esophageal tract for developing cancer[32,34]. Chronic inflammation caused by *H. pylori* or increased exposure to carcinogens via destroyed mucosal and immune barriers may play a role in laryngeal cancers. In the literature, there are several studies that point out the potential role of *H. pylori* infection in laryngeal carcinoma, with conflicting results[35-38]. In a case-control study, titers of *H. pylori* IgG were assayed by a serum enzyme linked immunoabsorbant assay (ELISA) method in 26 patients with SCC of the larynx (SCCL) and 32 controls with no history of any carcinoma. The results showed that the rate of seropositivity for *H. pylori* was significantly higher in SCCL (73%, 19/26) than in the control group (41%, 13/32). Accordingly, the authors suggested that *H. pylori* may be an initiator/promoter organism, but not the sole causative agent of SCCL[36].

In another study, 61 patients with severe laryngeal dysplasia or frank carcinoma of the head and neck were investigated for the presence of antibodies against *H. pylori.* The prevalence of *H. pylori* antibodies was significantly higher in the experimental group (63.0%) than the control group (40.7%). Based on the higher rate of seropositivity for *H. pylori* in the patient group, the authors suggested that *H. pylori* may have a positive role in laryngopharyngeal carcinoma[38]. Similarly, a prospective controlled study showed relatively higher *cagA* gene positivity in *H. pylori* in laryngeal cancer tissues and demonstrated that the presence of *cagA* gene in tissues was associated with lower survival rates and higher recurrence rates. The authors concluded that *H. pylori* is a possible carcinogen in laryngeal cancer development[39].

In a comprehensive case-control study, *H. pylori* was detected with PCR in laryngeal mucosa and serum antibodies were detected using ELISA. The presence of *H. pylori* was significantly more common in the laryngeal cancer group (n=81) than controls (n=75). Therefore, the authors suggested that the reason of *H. pylori* existence in larynx mucosa causes transportation to other sites of the body and concluded that *H. pylori* may be a promoter of SCCL[40]. Moreover, to observe the relationship between *H. pylori* and both benign and malignant laryngeal lesions, PCR was used to show 80.9% positivity in laryngeal cancer patients, whereas no positive result was found in benign laryngeal mucosal diseases[41].

In contrast to these studies, some investigators did not observe a correlation between *H. pylori* and laryngeal cancer. The role of *H. pylori* was compared in SCCL patients (n=31) and patients with benign laryngeal pathologies (polyp or nodule) (n=28) by microlaryngoscopic biopsies. *H. pylori* IgG antibody in serum samples was detected using ELISA and tissue samples were analysed with immunohistochemical examination. Serum IgG antibody positivity rates were similar in both the malignant and benign laryngeal lesion groups, and immunohistochemical analysis for *H. pylori* existence was negative in both groups. According to these results, the authors concluded that *H. pylori* infection was not involved in the pathogenesis of laryngeal cancers and was not a reservoir for *H. pylori* colonization[42]. Similarly, 74 patients with laryngeal cancer who underwent total/partial laryngectomy were evaluated for the existence of *H. pylori* both by real-time PCR method and histopathological evaluation. The positive control group consisted of patients with chronic active gastritis with histologically proven *H. pylori* positivity. The authors reported that PCR was positive for *H. pylori* in only one patient in the laryngeal cancer group, and when this positive case was reevaluated by immunohistochemical and histopathological analysis, *H. pylori* could not detected. Therefore, the authors concluded that *H. pylori* might not contribute to the pathogenesis of laryngeal carcinoma[43].

In another study, *H. pylori* was detected by histological examination under a light microscope in 69 total laryngectomy specimens pathologically diagnosed as SCCL and 30 laryngeal tissue samples diagnosed as non-neoplastic disease of larynx. However, it was reported that the results did not offer any clues

regarding the possible etiological association between *H. pylori* and SCCL[37]. Other studies also failed to show any evidence indicating that *H. pylori* may be an etiologic factor or have a role in the pathogenesis of laryngeal cancer or benign mucosal lesions[32,43,44].

Association between *Helicobacter pylori* and Pharyngeal Benign Lesions and/or Cancers

The causative, etiological, or pathological role of *H. pylori* infection in benign pharyngeal diseases (*e.g.,* acute or chronic pharyngitis) remains ambiguous. Several studies have investigated the presence of *H. pylori* in the oral cavity using different methods. Some of them detected *H. pylori* in the oral cavities of patients with halitosis, aphthous stomatitis, and periodontal disease[45,46]. Contrary to these studies, other investigators reported low prevalence of *H. pylori* in the oral cavity and concluded that the oral cavity is not a significant environment for this bacterium[2,47,48]. It has also been stated that the oral cavity and pharynx may act as an extragastric reservoir for *H. pylori* infection and that *H. pylori* may be regarded as a member of the normal flora of the mouth due to its presence in nearly all study populations[2,49]. Chronic pharyngitis patients (n=50) was assessed for the existence of *H. pylori* in the pharyngeal mucous membrane by template-directed dye-terminator incorporated with fluorescence polarization detection (TDI-FD) and modified Giemsa staining. *H. pylori* positivity was found in 38% of the cases with TDI-FD and in 8% of the cases with Giemsa stain. Therefore, the authors concluded that *H. pylori* may be related to chronic pharyngitis[50].

In terms of malignant diseases, some authors suggested a possible association between *H. pylori* and oral cancer[2]. In a case-control study of 20 patients with newly diagnosed oral cancer and 20 healthy controls without cancer, *H. pylori* identification was performed with culture and PCR analysis. *H. pylori* was detected in three patients in the case group and two patients in the control group by real-time PCR analysis, and in three patients in the case group and one patient in the control group by culture. Although statistically significant results were not observed, the authors suggested a possible association between *H. pylori* and oral cancer[51]. In addition, *H. pylori* positivity was demonstrated in 58 patients with oral SCC by analyzing oral swabs with both real-time PCR and culture[52]. In another study, *H. pylori* was detected in 191 patients with oral SCC and the prevalence of *H. pylori* was determined as 21.5% using immunohistochemical analysis. The authors also reported that patients with *H. pylori* expression have worse survival rates in comparison with patients without *H. pylori* expression and suggested that *H. pylori* expression in oral SCC might have an impact on disease-free survival[49]. But despite the significant results of these studies, further carefully designed cohort studies with larger samples are needed to confirm and quantify this possible association more precisely.

In a cross-sectional case-control study, *H. pylori* existence was studied in 98 previously untreated laryngohypopharyngeal carcinoma patients (*e.g.,* glottic or supraglottic larynx and hypopharynx cancer) whose diagnoses were confirmed histologically as SCC and 105 healthy (cancer-free) patients as a control group. The patients were divided into three groups: control (n=105), laryngeal cancer (n=70) and hypopharyngeal cancer (n=28). Sex, smoking status, site of tumor, and *H. pylori* status were selected as analysis criteria. The amount of IgG antibody against the high-molecular-weight cell-associated proteins of *H. pylori* was determined using ELISA. The results showed that seropositivity was significantly less common in the control group than the cancer groups, but did not differ significantly between the laryngeal and hypopharyngeal cancer groups. The authors also noted that the effect of smoking and *H. pylori* seropositivity remained highly significant rather than alcohol consumption. As a result of this study, the authors concluded that *H. pylori* infection is an independent risk factor for laryngohypopharyngeal carcinoma in the upper aerodigestive tract by disrupting mucosal barriers, impairing immune barriers, and allowing direct contact of the laryngohypopharynx with known carcinogens such as tobacco and alcohol[33]. Similarly, in a pilot case-control study, patients with histologically confirmed untreated laryngeal or pharyngeal (oropharyngeal or hypopharyngeal) SCC were evaluated for the effect of *H. pylori* infection in comparison with cancer-free controls. The authors concluded that *H. pylori* neither protected against nor enhanced laryngopharyngeal SCC, especially in pharyngeal cancers[53]. In contrast to these studies, an evaluation comparing *H. pylori* IgG seropositivity in 21 patients with SCC in the head and neck region (including oral cavity n=9, oropharynx n=1, hypopharynx n=2, and larynx n=9) with a control group (n=20) showed higher seropositivity in the control group (62%) rather than the cancer group (57%). Therefore, the authors concluded that *H. pylori* did not play an etiologic role in SCC[54]. Similar to this study, a case-control study was designed to evaluate the correlation between *H. pylori* infection and malignant neoplasm of the laryngopharyngeal mucosa and also determine the role of *H. pylori* in the prognosis, outcomes, and recurrence rates in these neoplasms. The study group included 80 patients diagnosed with laryngohypopharyngeal carcinoma (laryngeal n=68, hypopharyngeal cancer n=12) and the control group included 20 healthy patients and 10 patients with Reinke edema. *H. pylori* positivity was determined by using serological test (ELISA for IgG) and the patients were followed for five years. According to the results of the study, the authors reported a positive association between *H. pylori* infection and laryngopharyngeal cancers, whereas the presence of *H. pylori* infection was not associated with poor outcome or higher recurrence rates[55].

Conclusion

Helicobacter pylori is a well-known microorganism which can be localized in the stomach and different tissues of the body. Association between *H. pylori* infection and some gastrointestinal diseases (benign/or malignant) has been demonstrated. Systemic immune and inflammatory responses to *H. pylori* have been reported to cause some systemic diseases as well as different types of malignancies. However, the relationship between *H. pylori* and especially malignancies of the potential extragastric reservoirs remains controversial[2]. Although the association between *H. pylori* and upper and/or lower respiratory diseases is still debated, some reported findings support a positive correlation[2]. Further comprehensive studies with large and well-defined disease and control groups or prospective cohort data, are needed to prove the role of *H. pylori* in benign and/or malignant lesions of upper and/or lower respiratory tract.

Ethics

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: T.B., Y.B., Design: T.B., Y.B., Data Collection or Processing: İ.D., B.O., Analysis or Interpretation: T.B., Y.B., Ç.F.K., İ.D., B.O., Literature Search: T.B., Y.B., Ç.F.K., İ.D., B.O., Writing: T.B., Y.B., Ç.F.K.

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